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Editorial

The Pressing Need to Redefine "COPD"

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; COPD Genetic Epidemiology, **COPDGene®**; forced expiratory volume in 1 second, **FEV_1**; forced vital capacity, **FVC**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; computed tomography, **CT**; preserved ratio-impaired spirometry, **PRISm**

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Introduction

Chronic obstructive pulmonary disease (COPD) has now become a global epidemic, affects over 300 million individuals world-wide, has become the third most common cause of death and is one of the leading causes of chronic morbidity and hospitalization, resulting in an enormous economic burden. This special issue of *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation* includes 3 important new analyses of the large COPD Genetic Epidemiology (COPDGene®) cohort concerning diagnosis, progression and the consequences of this disease. These striking new data have important implications for how we should define COPD in the future and how we should recognize different phenotypes. This will also be important in directing a search for new disease-modifying therapies that are likely to be most effective in early disease.[1] The new data have important implications for health care providers, particularly general practitioners, for regulators and, most importantly, for patients.

The diagnosis of COPD has relied on the demonstration of fixed airflow obstruction using spirometry, with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of < 0.7 and the importance of spirometry has been emphasized in the Global initiative for chronic Obstructive Lung Disease (GOLD) management strategy and in all COPD recommendations.[2] However, it is well recognized that some smokers may have significant symptoms, such as mucus hypersecretion/chronic bronchitis, dyspnea, cough and acute events similar to COPD exacerbations, as well as typical computed tomography (CT) changes of emphysema, gas trapping and airway wall thickening that are typically found in COPD patients, despite having an FEV_1/FVC ratio of ≥ 0.7.[3-5] Indeed, these individuals may often be treated and respond to COPD therapies such as bronchodilators. These individuals have sometimes been called GOLD 0 or pre-COPD, which was thought to be a population at risk of developing spirometrically-defined airflow obstruction in the future. It seems likely that GOLD 0 stage includes patients with small airway obstruction that is not yet detectable by spirometry as FEV_1 predominantly measures large airway obstruction and may only become abnormal late in the course of the disease. There is compelling evidence that small airway disease is present in mild COPD, with a loss of small airways and narrowing and thickening of others.[6,7] For

many years it has been recognized that some smokers with normal spirometry have abnormalities in tests of small airway function, such as nitrogen washout. Other smokers with symptoms have a reduced FEV_1 but normal FEV_1/FVC ratio, which has been termed preserved ratio-impaired spirometry (PRISm), which often appears to progress to GOLD 2–4 stages over time with increased mortality in the COPDGene® cohort.[8] This has been confirmed in a large independent population cohort from the Netherlands, which found that of participants initially classified as PRISm, about half progressed to COPD GOLD stages 2–4, over 5 years, with increased cardiovascular mortality and frequent cardiovascular comorbidity, whereas other participants had persistent PRISm but a normal age-related decline in lung function.[9] The pathology of PRISm is not yet known, but it is likely that these patients have small lungs together with small airway obstruction.

COPDGene® is a cohort which recruited over 10,000 current or former cigarette smokers (>10 pack years) who have been studied at baseline and after 5 years, with an ongoing further assessment at 10 years and in whom interstitial lung disease and predominant bronchiectasis were excluded.[10] In the study of Lowe et al (with over 100 authors) over 8000 smokers were analyzed for symptoms, CT abnormalities consistent with spirometric COPD, disease progression and all-cause mortality. Using the GOLD diagnostic criteria, about half of the participants would be classified as having COPD, but if symptoms and CT abnormalities are included, over 80% may be classified as having COPD. The more criteria that were consistent with COPD, the greater was the disease progression (measured at 5 years in about half of these participants) and the mortality risk.[11] This could have profound implications for the future diagnosis of COPD as, at least in heavy current and former smokers, individuals with normal spirometry and no evidence of airway obstruction can still have the typical clinical features and lung structural abnormalities that are seen in COPD patients diagnosed by a FEV_1/FVC ratio of <0.7, as currently recommended in the COPD Guidelines. Furthermore, these patients have a similar risk of progression and mortality and may represent around 40% of patients.

The case for widening the criteria for diagnosing COPD is enforced by the 2 additional analyses included in this issue. Young et al looked at how the airway-predominant and emphysema-predominant CT patterns related to disease progression and mortality in over 4000 patients in the COPDGene® cohort who had baseline and 5-year CT scans.[12] Airway-predominance was associated with conversion from GOLD 0 to PRISm and GOLD 0 to GOLD 2–4 stages, but not to GOLD stage 1. By contrast, emphysema-predominance was linked to progression from GOLD 0 to GOLD stage 1 and from GOLD 1 to GOLD 2–4 stages. Conversion from PRISm to GOLD 2–4 (over 30%) occurred with both CT patterns. Interestingly, smoking cessation between the initial measurements and 5 years was associated with reduced progression mainly in patients with GOLD 0 and GOLD 1 stages COPD, so future therapies that target disease progression will likely be most effective in early disease. Patients with airway-predominant disease and emphysema-predominant disease who progress have a high 5-year all cause-mortality. Future therapies will need to differentiate these 2 disease patterns, with targeting of small airway fibrosis in the airway-predominant patients and targeting alveolar destruction in emphysema-predominant patients.

The link between pathophysiological phenotype and mortality is further explored in this issue's third original research article, which shows that the top 2 deciles of airway-predominant and emphysema-predominant disease were associated with a high all-cause mortality (26% and 21%, respectively), which was even higher (54%) in those with combined disease patterns.[13] The airway-predominant group had a greater disease severity, was associated with PRISm and had a great risk of cardiovascular mortality in addition to respiratory mortality. The emphysema-predominant group had higher FEV_1 values and included more patients in GOLD 0-2 stages. Interestingly, from a panel of blood biomarkers, the airway-predominant group was linked to a higher C-reactive protein, whereas in the emphysema group soluble receptor for advanced glycation end products, sRAGE, was higher. More research is needed to explore the clinical value of these biomarkers.

These new analyses of the COPDGene® cohort could have important implications for diagnosis and disease classification, for management and for the future development of therapies that may prevent COPD progression and mortality. The studies show very clearly that smokers in the COPDGene® cohort who do not fulfill the current spirometric criteria for

a diagnosis of COPD (GOLD stage 0 and PRISm) may progress to spirometric COPD through different trajectories and have an increased risk of death. The authors suggest that the COPDGene® 2019 criteria, that includes exposure to a risk factor (smoking), airway obstruction measured by spirometry, symptoms and CT abnormalities, should all contribute to the diagnosis. This raises the issue of terminology as these groups with an $FEV_1/FVC \geq 0.7$ do not have obstruction, so perhaps should be called *CoPD*, pre-obstructive COPD or pre-COPD (by analogy to prediabetes in those with abnormal glucose tolerance).[14] This new approach to diagnosis is easy to apply in hospital clinics, where CT scanning is readily available, and many patients already have routine low dose CT scans performed. However, it may be more difficult to implement in general practice, where most patients with early COPD are seen.

It is important to realize that there are some significant limitations to the COPDGene® studies when studying the natural history of the disease. The individuals included in the cohort constitute a "convenience cohort". They were heavy smokers with an average exposure of ~50 pack years and the prevalence of airflow limitation is much higher than in a general population. The demonstrated associations and trajectories may therefore not be similar in a general population, in the many patients with lower tobacco exposures and in those with COPD without tobacco exposure. COPD may occur in non-smokers due to exposure to occupational dusts, biomass smoke and outdoor air pollution.[15,16] While these patients account for < 20% of COPD patients in Western counties they may account for around half of the diagnosed COPD patients in low- and middle-income countries. COPD associated with biomass smoke is more likely to be associated with small airway disease than emphysema, but it has not been explored how common PRISm and GOLD stage 0 is in these populations (usually women). Finally, more studies are needed of small airway function in early COPD, as this may be abnormal long before FEV_1 declines. Impulse oscillometry to measure peripheral airway disease is easy for patients to perform and now more widely available with less expensive analysers also becoming available.[17] Relying on CT to do this may prove difficult in clinical practice and alternative approaches like oscillometry, a non-invasive measurement of lung mechanics during tidal breathing, which correlates with CT-measured gas trapping, are now being investigated.[18] However, longitudinal studies and measurement in large populations is needed to further evaluate the usefulness of this test in clinical practice.

COPDGene® has greatly increased our knowledge of the way in which COPD evolves with numerous publications on this topic arising from the many analyses of these data.[19] Some investigators have used different CT algorithms from those described in the 3 papers reported here and have applied machine-learning to describe different trajectories of disease development.[20,21] The COPDGene® investigators would do the field a great service if they could arrive at a consensus on the most appropriate way of describing their data that could then be applied to other data sets to confirm their observations. Hopefully this will happen in the near future. One thing is clear after reading these 3 papers. We need large population-based longitudinal studies with detailed assessment at both baseline and follow-up. However, these are costly and time-consuming. While waiting for these, we will not be doing patients a favor by sticking with the old concept of viewing decline in FEV_1 as the only measure of disease activity and disregard COPD-like symptoms and imaging in those smokers not fulfilling the traditional diagnostic criteria for COPD. We need bold new studies applying different criteria for inclusion and we need more research into the mechanisms of early COPD.

Declaration of Interest

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